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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/501,284	02/07/2005	Gesine Schliecker	I-2002.001 US	5686

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Intervet/Schering-Plough Animal Health
Patent Dept. K-6-1, 1990
2000 Galloping Hill Road
Kenilworth, NJ 07033-0530

EXAMINER	
PERREIRA, MELISSA JEAN	

ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
03/17/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ahpatentsus@merck.com

Office Action Summary	Application No.	Applicant(s)	
	10/501,284	SCHLIECKER ET AL.	
	Examiner	Art Unit	
	MELISSA PERREIRA	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 December 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19 and 21-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19 and 21-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-19 and 21-26 are pending in the application. Any objections and/or rejections from previous office actions that have not been reiterated in this office action are obviated.

New Grounds of Rejection Necessitated by the Amendment to the Claims

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-19 and 21-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krone et al. (US 5,391,696), DiBenedetto et al. (*Polymer Degrad. Stab.* **1994**, *45*, 249-257) and Goepferich, Handbook of Biodegradable polymers, Mechanism of Polymer Degradation and Elimination, Harwood Academic, Amsterdam, 1998, p451-471 in view of Suzuki et al. (US 6,015,789), Remington's Pharmaceutical Sciences **1990** 18th Ed. Chpt. 89 and Lewis (US 5,838,571).

3. Krone et al. (US 5,391,696) discloses formulations comprising a.) polytartrate polymer, such as (2',3'-(1',4'-diethyl)-L-tartyl poly-(2,3-O-isopropylidene)-L-tartrate) condensates; b.) buserelin; c.) polyethylene glycol and d.) pharmaceutically acceptable excipients, etc. (abstract; column 10, lines 36-45 and 54-59). The formulations of the disclosure may be formed via compaction/compression and do not comprise a barrier

structure (abstract; column 1, lines 9-14; column 2, lines 21-27; column 11, lines 35-40). The formulations are used for diagnostic and therapeutic methods (e.g. tablets, etc.) wherein they are suitable for visualization of cavities in humans, etc. (column 11, lines 19-52).

4. The polycondensates have low swelling power and are easily degradable chemically or biologically to essentially non-toxic products and whose degradation products are water-soluble (the polymer will dissolve and be broken down into toxicologically harmless products in the course of time under physiological conditions)(column 2, lines 9-16). The degradation proceeds via functional side groups, ring opening and parent chain degradation (column 11, lines 41-50; table 1).

5. Krone et al. teaches that the polytartrate preparations have a decreased "initial burst" which implies that there is a second release of active agent (column 2, lines 21-27). The release rate of the "secondary burst" of the instant claims is defined as occurring over 2-4 days in the specification (specification p15, lines 10-12) and therefore the second release of active agent of Krone et al. encompasses the "secondary burst" of the instant claims as it may be a prolonged release showing uniformly controllable active substance release (column 2, lines 21-27).

6. The reference of Krone et al. does not explicitly disclose three phases of the pulsatile release or that the onset of the second burst is accompanied by dehisce of the tablet.

7. DiBenedetto et al. (*Polymer Degrad. Stab.* **1994**, *45*, 249-257) discloses the release of both high and low molecular weight substances from a series of

biodegradable poly(alkylene tartrates) (e.g. tablets) wherein the relationship between chemical compositions and the release rate of the compounds were examined. The hydrophilic/hydrophobic properties of the polymer can be easily varied by changing the chain length of the alkylenediol. The molecular weight distributions of the polymers, the hydrophilic character of the polymers, and the porosity of the matrices influenced the release rates of the model compounds (abstract; p249, Introduction).

8. DiBenedetto et al., also, discloses that there are at least two, and perhaps three, phases of release involved (i.e. pulsatile). The first was a lag phase. The second phase was predominant and had a square root of time dependence that implied Fickian, or quasi-Fickian, diffusion controlled the release and during the third period the nearly convex curvature of the release versus square root of time curve implied a decrease in the apparent Fickian diffusion coefficient (p252, right column).

9. The rate of water uptake increased as the hydrophilic character of the polymers increased. In all cases there was an initial period of rapid uptake (p254, left column). The tablet porosity also influenced the water uptake wherein the initial period of rapid water uptake was due primarily to the diffusion of water into the pores of the tablet. Substance release is dependent on the rate of water uptake (p255, right column).

10. Goepferich discloses that the degradation rate and erosion of biodegradable polymers increases when raising the content of the hydrophilic component (p455, water uptake, p459, first paragraph; p467, summary). Figures 1-3 show representations of erosion. pH is one of the most important factors of hydrolytic polymer degradation. pH changes can modify hydrolysis rates by orders of magnitude (p456, pH).

11. At the time of the invention it would have been obvious to one ordinarily skilled in the art that the polytartrate preparations of Krone et al. will have two release phases (bursts) wherein a majority of the active agent is released in a pulsatile manner as DiBenedetto et al. teaches that there is at least two, and perhaps three, phases of release involved with polytartrate preparations.

12. Also, at the time of the invention it would have been obvious to one ordinarily skilled in the art that (at least a portion of) the tablet will dehisce at the onset of the second release of active agent as the polytartrate preparations of Krone et al. degrade over time and the hydrophilicity of the polymer and pH affects the erosion behavior of polymers substantially (Goepferich). Thus, the degradation is expected to occur at various time points during the release of the active agent and the hydrophilicity of polymer can be predictably modified to provide for a desired degradation rate.

13. In regards to the "lag time" the specification recites (p13, lines 17-20 and 30-33), "a secondary "lag phase" of ***low or no*** release of the drug followed by a second burst". Therefore, at the time of the invention it would have been obvious to one ordinarily skilled in the art that the polytartrate tablet formulations which are prepared via compaction/compression of Krone et al. encompass the composition of the instant claims as they have a first "initial burst", a second release of active agent (burst) and the phase between the bursts (i.e. lag phase) wherein the lag phase may release drug. DiBenedetto et al. teaches of a third phase/second release of substance after the second phase/first release of substance which provides for a lag phase between where

there is a low release of drug. Therefore, the time between release/bursts of the polytartrate formulations of Krone et al. encompass the "lag phase" of the instant claims.

14. The combined reference of Krone et al., DiBenedetto et al. and Goepferich do not disclose the GnRH agonist nafarelin, the method of administering the pharmaceutical composition or the process for preparing the pharmaceutical composition of the instant claims.

15. Suzuki et al. (US 6,015,789) discloses a pharmaceutical composition/solid tablet preparation comprising a GnRH agonist, such as buserelin or nafarelin; pharmacologically acceptable carrier; etc. for administration to a human being to treat sex hormone-dependent disease (claims 1,2; column 97, lines 63-66; claim 2; column 98, lines 17-25; column 101; column 102, lines 45-55). The pharmaceutical composition/solid tablet preparation comprising excipients (i.e. polyethylene glycol) are prepared via compression (column 99, lines 23-33).

16. Remington's Pharmaceutical Sciences **1990** 18th Ed. Chpt. 89 discloses the preparation of oral solid dosage forms from granulation techniques which involve mixing the materials, sieving the mixture and shaping the mixture with tableting equipment (especially see p1634; methods of preparation p1641-1646).

17. Lewis (US 5,838,571) discloses that standard tablet compression force of a conventional tablet is in the range of 18 to 27 kN (column 13, lines 1-7).

18. At the time of the invention it would have been obvious to one ordinarily skilled in the art to substitute one GnRH agonist, such as buserelin of Krone et al. for an

equivalent GnRH agonist, such as nafarelin of Suzuki et al. in the polytartrate solid tablets (prepared via compression) of the combined reference of Krone et al., DiBenedetto et al. and Goepferich as it is obvious to those skilled in the art to make known substitutions on compounds that are similar in structure and function to observe the effects on the function of such compounds and to use the observations/data to further manipulate a compound to generate the desired effect, such as treat a sex hormone-dependent disease. Suzuki et al. teaches of the administration of nafarelin or buserelin preparations to humans and therefore it would have been obvious to one skilled in the art to administer a polytartrate composition comprising nafarelin or buserelin to a human for the controlled release of the nafarelin to treat a sex hormone-dependent disease.

19. Remington's pharmaceutical sciences teaches of standard oral tablet formation involving mixing the components of the composition, sieving and compressing with tableting equipment and therefore it would have been obvious and predictable to one ordinarily skilled in the art to use the standard techniques of Remington's for the compressed tablet polytartrate compositions of Krone et al. as the result is a compressed tablet formulation.

20. The standard compression force for the preparation of a conventional tablet is in the range of 18 to 27 kN as taught by Lewis and therefore the polytartrate solid tablets (prepared via compression), which do not comprise a barrier structure encompass the composition of the instant claims which is prepared via compression with a compression force from 10 to 65 kN/cm^2. The simple compression of polytartrate compositions

provides for release of the pharmaceutically active material in a pulsatile manner as evidenced by the specification (specification p3, lines 28-33).

21. The formulation of the combined disclosures encompasses the composition of the instant claims and is capable of the same functions, such as forming degradation products that increase the pressure inside the composition and has the same properties, such as a glass transition temperature that is greater than 40°C. Therefore, the burden is shifted to applicant to show that the pharmaceutical composition of the instant claims is materially different than the polytartrate polymer formulation of Krone et al.

22. It is respectfully pointed out that instant claims 1-13 and 22-23 are product-by-process limitations. Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed Cir. 1985). See MPEP 2113.

23. Also, the recitation, "determining a time of the lag phase", is a mental step and does not contain any active technique (manual steps) for determining a time of the lag phase. There are no specific active steps to define how such determining is performed or which limit the amount of time of the lag phase.

Response to Arguments

24. Applicant's arguments filed 12/28/10 have been fully considered but they are not persuasive.

25. Applicant asserts that the references themselves nor the inferences and creative steps that a person of ordinarily skill in the art would have employed at the time of the invention or suggested a polytartrate composition "wherein the onset of the second burst is accompanied by dehisce [(rupturing or breaking open)] of the tablet" as recited in the amended claims.

26. The reference of Krone et al. teaches that polycondensates are have low swelling power and are easily degradable chemically or biologically to essentially non-toxic products and whose degradation products are water-soluble (the polymer will dissolve and be broken down into toxicologically harmless products in the course of time under physiological conditions). The degradation proceeds via functional side groups, ring opening and parent chain degradation.

27. DiBenedetto et al. teaches of a series of biodegradable poly(alkylene tartrates) (e.g. tablets) wherein the hydrophilic/hydrophobic properties of the polymer can be easily varied by changing the chain length of the alkylenediol. The molecular weight distributions of the polymers, the hydrophilic character of the polymers, and the porosity of the matrices influenced the release rates of the model compounds

28. The rate of water uptake increased as the hydrophilic character of the polymers increased. In all cases there was an initial period of rapid uptake. The tablet porosity also influenced the water uptake wherein the initial period of rapid water uptake was

due primarily to the diffusion of water into the pores of the tablet. Substance release is dependent on the rate of water uptake.

29. Goepferich discloses that the degradation rate and erosion of biodegradable polymers increases when raising the content of the hydrophilic component. pH is one of the most important factors of hydrolytic polymer degradation. pH changes can modify hydrolysis rates by orders of magnitude.

30. At the time of the invention it would have been obvious to one ordinarily skilled in the art that the polytartrate preparations of Krone et al. will have two release phases (bursts) wherein a majority of the active agent is released in a pulsatile manner as DiBenedetto et al. teaches that there is at least two, and perhaps three, phases of release involved with polytartrate preparations.

31. Also, at the time of the invention it would have been obvious to one ordinarily skilled in the art that (at least a portion of) the tablet will dehisce at the onset of the second release of active agent as the polytartrate preparations of Krone et al. degrade over time and the hydrophilicity of the polymer and pH affects the erosion behavior of polymers substantially (Goepferich). Thus, the degradation is expected to occur at various time points during the release of the active agent and the hydrophilicity of polymer can be predictably modified to provide for a desired degradation rate.

Conclusion

32. No claims are allowed at this time.

33. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MELISSA PERREIRA whose telephone number is (571)272-1354. The examiner can normally be reached on 9am-5pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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